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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/725,221	12/01/2003	Donald E. Frail	PC 27831 (01457.US1)	2133

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WARNER-LAMBERT COMPANY
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EXAMINER

GEMBEH, SHIRLEY V

ART UNIT	PAPER NUMBER
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1614

DATE MAILED: 09/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/725,221

Applicant(s)

FRAIL ET AL.

Examiner

Shirley V. Gembeh

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 December 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-37 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-37 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>6/14/04</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Information Disclosure Statement

The information disclosure statement (IDS) submitted on June 14, 2004 has been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The specification while being enabling for the method for treating said disorders include, without limitation, chronic and neuropathic pain, migraine therapy, urge, stress and mixed urinary incontinence. The compounds provided herein, are particularly useful in the treatment of these and other disorders due, at least in part, to their ability to selectively bind to the transporter 5 proteins for certain neurochemicals with a greater affinity than to the transporter proteins for other neurochemicals does not enable any person skilled in the art to which it pertains, or which it is most nearly connected to practice the invention commensurate in scope with these claims does not reasonably provide enablement for prevention. Thus noted the term "prevent" does not necessarily mean that the something is kept from ever occurring, but it is kept an interpretation that falls under the "broad and reasonable " standard for claim interpretation as set forth in the MPEP at § 2111 and thus is proper.

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In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed and 8) the relative skill of those skilled in the art.

1) The nature of the invention: The method of use claims are drawn to preventing an individual from having chronic pain but no working examples are given to support applicants claim.

2) The state of the prior art: A study by Couch et al, *Neurology* (1976) 26 (121-127) that amitriptyline result section indicates page 123 shows that amitriptyline had a prophylactic effect that is not related to severity of migraine also see graph on page 123. The graph indicates that the prophylactic effects were unable to prevent headache (condition where there is pain).

3) The predictability or lack thereof in the art: Pharmacological activity in general is a very unpredictable area as discussed above. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: In addition there is no apparent guidance as to what to expect or

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how to extrapolate prevention that would 'a priori' have been expected to have produced the claimed result as claimed.

6) The breadth of the claims: The claims are drawn to methods of preventing,

7) The quantity of experimentation needed would be undue burden since there is inadequate guidance given to the skilled artisan for the reasons stated above.

8) The relative skill of those skilled in the art. Based on the unpredictable nature of the invention, one skilled in the art would not have envisioned practicing the invention without the exercise of undue experimentation burden.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims.

In consideration of each of factors 1-8, it is apparent that there is undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue and the resultant outcome not predictable.

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-37 are rejected under 35 U.S.C. 102(a) and (e) as being anticipated by

Beck et al., US 2002/0091134.

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Beck discloses compounds of formula I, II, III and IV at § 0005 as in claim 1-37 drawn to a therapeutic compound administered to patients for the treatment of various neurological disorders. The reference anticipates the claimed invention of claims 1-37 as various neurological disorders encompasses a variety of diseases including migraine headache (see abstract). Consequently, the reference anticipates the claimed invention defined, the method of use does not alter the composition.

Claim Rejections - 35 USC § 103

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

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Claims 1-37 are rejected under 35 U.S.C. 103(a) as being obvious over Boltze et al., US 4,564,613 ('613), Beck et al., US 6,579,885 ('885) and Blacks' Medical Dictionary, © 2002 A & C Black Publishers LTD. (Migraine-Neurological Diseases and Disorders).

Beck teaches compounds of formula I, II, III and IV at § 0005 as in claim 1-37 drawn to a therapeutic compound administered to patients for the treatment of various neurological disorders.

Boltze et al., teach, a pharmaceutical composition comprising (column 1 line 10) pyrodindoles to treat diseases of the central nervous systems (claim 1) column 1 line 8-9, i.e. the same compound administered in the claim by applicant. Central nervous system (CNS) disease includes a number of diseases associated with the CNS, such as headache, migraine and Pain.

Beck did not per se teach treatment of headache, migraine or chronic neuropathic pain. The claims differ since the '885 patent uses phenyl substituted tetrahydroisoquinolines derivatives to treat various neurological disorders, and did not per se teach of the treating headache or migraine, however migraine and headache is considered to be a neurological disorder, as taught by Blacks' Medical Dictionary.

Beck et al., however, teach the use of the pharmaceutical compound administering the compound aryl and heteroaryl substituted tetrahydroisoquinoline column 2 line 52-53. , i.e. the structurally similar compound administered in the claim by applicant.

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It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of '613 and '885 since the compounds are structurally the same with effectively the same moieties, would administer it for the treatment of pain (migraine) since neurological disorder can also include pain (migraine/headache) for the same reasons as discussed above.

One of ordinary skill in the art would have known that using 4-phenyl substituted tetrahydroisoquinolines derivatives in place of heteroaryl substituted tertadriisoquinoline would work because is a well known compound for treatment of neurological disorders, and pain is classified as a neurological disorder.

Therefore one of ordinary skill would have been motivated to combine the teachings of '613 with that of '885 as disclosed for the treatment of CNS associated diseases or disorders.

The cited prior art would have motivated one of skill in the art to select for neuropathic pain.

One of ordinary skill in the art would have expected successful results for the treatment of chronic neuropathic pain. Thus the claims are deemed prima facie obvious over the cited prior art.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an

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invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(I)(1) and § 706.02(I)(2).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

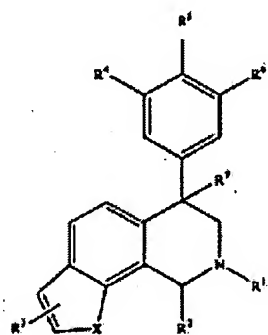
A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

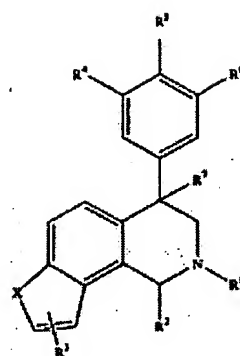
Claims 1-37 are provisionally rejected under the judicially created doctrine of double patenting over claims 1-32 of copending Application No.09902845. This is a provisional double patenting rejection since the conflicting claims have not yet been

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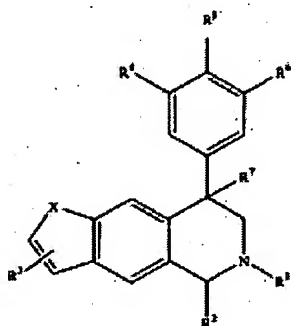
patented. The formula/compound of the claimed invention is identical to the co-pending application, as shown here as IA, IB, IIA IIB, IIIA and IIIB.



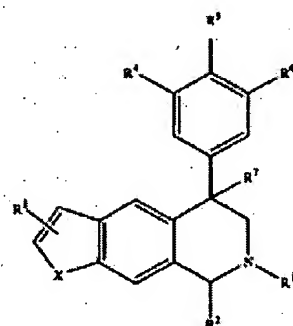
IA



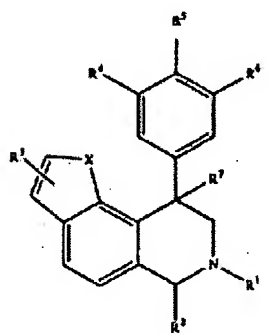
IB



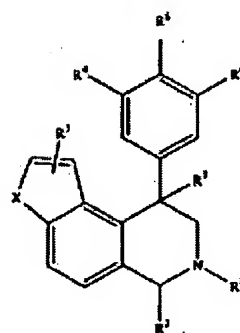
IIA



IIB



IIIA



IIIB

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Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending application are to a pharmaceutical composition/compound reciting the identical structure which comprises of an active compound phenyl substituted tetrahydroisoquinolines. The moieties attached are effectively the same in the current and copending applications. The subject matter claimed in the instant application is fully disclosed in the referenced copending application, the only difference is in the use of treatment.

Thus, claims 1-37 are directed to an invention not patentably distinct from claims 1-40 of co-pending application.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shirley V. Gembeh whose telephone number is 571-272-8504. The examiner can normally be reached on 8:30 -5:00, Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SJS
SVG
08/26/05


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